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| 10/716,470 | 11/20/2003 | Yoshiya Gunji | US-103 | 5760 |

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CERMAK & KENEALY LLP
ACS LLC
515 EAST BRADDOCK ROAD
SUITE B
ALEXANDRIA, VA 22314

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| EXAMINER |
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RAMIREZ, DELIA M

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1652

DATE MAILED: 09/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

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|------------------------------|--------------------------------------|-------------------------------------|--|
| Office Action Summary | Application No. 10/716,470 | Applicant(s) GUNJI ET AL. | |
| | Examiner Delia M. Ramirez | Art Unit 1652 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 July 2006.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-9 is/are pending in the application.
- 4a) Of the above claim(s) 8 and 9 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 20 November 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date <u>12/21/04, 9/17/04, 4/6/04</u> . | 6) <input checked="" type="checkbox"/> Other: <u>Abstracts</u> |

DETAILED ACTION

Status of the Application

Claims 1-9 are pending.

Applicant's election with traverse of Group I, claims 1-7 drawn to a *Methylobacillus* bacterium which produces a protein involved in secretion of L-lysine, in a communication filed on 7/21/2006 is acknowledged.

Applicant's traverse is on the grounds that it would not pose an undue burden on the Examiner to examine all claims together, and that a search of the claimed inventions is not non-coextensive.

Applicant's arguments have been fully considered but are not deemed persuasive to withdraw the restriction requirement. A comprehensive search of all inventions is not co-extensive since literature providing information about the bacterium of Group I may not provide any information regarding the method for producing L-lysine of Group II, and vice versa. Furthermore, Groups I and II have different classes/subclasses. Thus, search and examination of all the inventions would impose an undue burden on the Office in view of the fact that the Examiner would have to perform separate searches for both inventions, which may be overlapping but not co-extensive.

The requirement is deemed proper and therefore is made FINAL.

Claims 8-9 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 1-7 are at issue and are being examined herein.

Specification

1. The abstract of the specification is objected to due to the recitation of "outside of a cell of a methanol-assimilating bacterium" for the following reasons. The term appears to imply that a bacterium has a cell, which is unclear and confusing since a bacterium is a unicellular organism. Appropriate correction is required.

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2. The specification and the abstract are objected to due to the recitation of the term "helixes". It is believed the correct spelling for the term is "helices". Appropriate correction is required.
3. The specification is objected to due to the recitation of "production of cysteine, cysteine" (page 2, last line). Appropriate correction is required.
4. Applicant's cooperation is requested in reviewing the specification for additional minor typographical/spelling errors and making the appropriate corrections.

Priority

5. Acknowledgment is made of a claim for foreign priority under 35 U.S.C. 119(a)-(d) to JAPAN 2002-336340 filed on 11/20/2002.

Information Disclosure Statement

6. The information disclosure statements (IDS) submitted on 4/6/2004, 12/21/2004, 9/17/2004 are acknowledged. The submissions are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Drawings

7. The drawings submitted 11/20/2003 have been reviewed and are approved by the Examiner.

Claim Objections

8. Claims 1-4 are objected to due to the recitation of the term "helixes". This appears to be a spelling error. It should be amended to recite "helices". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claim 1 (claims 2-6 dependent thereon) is indefinite in the recitation of “protein having a loop region and six hydrophobic helices...and wherein said variant does not contain said loop region” for the following reasons. One of skill in the art would interpret the term “loop” as encompassing any structure which does not have a defined secondary structure, such as that of an alpha helix or a beta sheet. Thus, in a protein comprising several alpha helices and/or beta sheets, one of skill in the art would consider any connecting segment between alpha-helices and/or beta sheets to be a loop. If the protein from which the variant derives comprises six hydrophobic helices, one would assume that there is at least 5 loops, each connecting the six helices. The claim refers to a variant lacking a loop region but comprising 6 helices. This is unclear since a loop would be required to join the 6 helices. For examination purposes, it will be assumed that the protein recited comprises six hydrophobic helices and the variant comprises the same six hydrophobic helices with modifications in the connecting segments. Correction is required.

12. Claim 2 is indefinite in the recitation of “substantially consists of” as this is a relative term and neither the claim nor the specification provide a standard for ascertaining the requisite degree. Therefore one of skill in the art cannot reasonably apprise of the scope of the invention. For examination purposes, no patentable weight will be given to the term. Thus, claims 1 and 2 will be considered duplicates. Correction is required.

13. Claim 3 is indefinite in the recitation of “wherein said variant has six hydrophobic helices” because it is unclear how the limitation recited further limits claim 1. It is noted that the “wild type” protein recited in claim 1 is a protein having a loop region and 6 helices and the variant of claim 1 is

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different from the “wild type” protein in that it lacks the loop region. Therefore, the variant of claim 1 still has 6 helices. For examination purposes, claims 1 and 3 will be considered duplicates.

14. Claim 4 is indefinite in the recitation of “wherein said variant is a complex comprising a peptide containing the first, second and third hydrophobic helices relative to the N-terminus, and a peptide containing the fourth, fifth and sixth hydrophobic helices relative to the N-terminus” for the following reasons. As written, the DNA in claim 1 encodes a single polypeptide which comprises a variant having six helices. Claim 4 as written requires a complex where two separate peptides are required. The term “complex” implies that the members of the complex are not necessarily physically linked in a single polypeptide (e.g., hydrogen bond). Therefore, the peptides in the complex can be encoded by two separate DNAs. If this is the case, the genus of variants of claim 1 does not encompass the complex of claim 4. As such, claim 4 does not further limit claim 1. For examination purposes, it will be assumed that claim 4 does not depend from claim 1. When possible, those limitations of claim 1 which are applicable to claim 4 will be included. Correction is required.

15. Claim 5 (claim 6 dependent thereon) is indefinite in the recitation of “protein is LysE protein” for the following reasons. As written, the term “LysE” appears to be generic and not limited to a specific organism. While the gene nomenclature used for the protein may be appropriate for the product of the LysE gene of *C. glutamicum*, the use of this nomenclature for proteins of identical function in other organisms may not be accurate. As known in the art, genes encoding proteins of identical function in two different organisms may use different designations. For example, the ARO4 gene of *Candida albicans* encodes a DAHP synthase whereas the *E. coli* counterpart is the aroF gene. See the abstracts of Sousa et al. (Microbiology 148(Pt5):1291-1303, 2002) and Weaver et al. (J. Bacteriol. 172(11):6581-6584, 1990). As such, the use of gene terminology which is applicable to some organisms and not to others is confusing since the claim uses this gene nomenclature with respect to any organism. It is noted that claim 6 is also indefinite in view of the fact that the claim recites the term “derived” which cannot be construed

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as limited to “isolated” since the term “derived” encompasses any number of modifications, thus it is not limited to proteins isolated from coryneform bacterium. For examination purposes, the terms “LysE protein” will be interpreted as “lysine transport protein”. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-4 as interpreted are directed to *Methylobacillus* cells able to produce L-lysine or L-arginine, wherein a genus of DNA molecules has been introduced, wherein said DNA molecules encode a genus of protein variants comprising six hydrophobic helices, wherein said helices can have any amino acid sequence, and wherein said protein variants are involved in secretion of L-lysine to the outside of a methanol-assimilating bacterium. Claims 5-6 are directed to the *Methylobacillus* cells of claim 1 with the added limitation that the protein variants are the variants of a lysine transport protein. Claim 7 is directed in part to *Methylobacillus* cells able to produce L-lysine or L-arginine, wherein a genus of DNA molecules has been introduced, wherein said proteins facilitate secretion of L-lysine and/or L-arginine to the outside of a methanol-assimilating bacterium, and wherein said DNA molecules encode a genus of proteins comprising SEQ ID NO:10 with any number of modifications, thus having any structure, See Claim Rejections under 35 USC 112, second paragraph, for claim interpretation.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that “A written description of an invention involving a chemical genus, like a description of a chemical species, ‘requires a precise definition, such as by structure, formula, [or] chemical name,’ of the claimed subject matter sufficient to distinguish it from other materials”. As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In the instant case, the claims encompass an extremely diverse genus of polynucleotides, both structurally and functionally. While the specification discloses that the polynucleotide of SEQ ID NO:9 encodes a polypeptide (SEQ ID NO: 10) that is a truncated form of the lysine transport protein of SEQ ID NO:8 (product of the *C. glutamicum* LysE gene), which is known to have six hydrophobic helices and a hydrophilic region between the third and fourth helices (from the N-terminus) at positions 94-145, and asserts that the polypeptide of SEQ ID NO:10 functions as a lysine transport protein in *Methylophilus* and *Methylobacillus* cells, the specification is completely silent regarding (1) the structural features required in any protein having six helices and involved in secretion of L-lysine to the extracellular medium, and (2) the functions of all proteins as recited involved in secretion of L-lysine. It is noted that while the genus recited require helices, the amino acid sequence of those helices presumably would determine their role in secreting L-lysine. It is not expected that any protein comprising 6 helices would be involved in

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secreting L-lysine. Furthermore, the claims encompass not only L-lysine transport proteins but rather any protein which has a role in secretion of L-lysine. This would encompass, for example, proteins which are transcription modulators of a gene encoding an L-lysine transport protein, or proteins which are enhancers of L-lysine transport proteins. However, the specification only discloses a single L-lysine transport protein.

While a sufficient written description of a genus of polynucleotides may be achieved by a recitation of a representative number of polynucleotides defined by their nucleotide sequence, or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus, in the instant case, there is no structural feature recited, nor there is any information as to a structure/function correlation that would describe the entire genus of polynucleotides required.

The genus of polynucleotides required is an extremely large structurally variable genus with the potentiality of encompassing different biological activities associated with secretion of L-lysine. While one could argue that the disclosure of the polypeptide of SEQ ID NO: 10 and the polynucleotide of SEQ ID NO: 9 provides adequate description for all the members of the genus, it is noted that the art teaches several examples of how even small changes in structure can lead to changes in function. For example, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that mutations which result in one conservative amino acid substitution transform a β -ketoacyl synthase into a malonyl decarboxylase and completely eliminate β -ketoacyl synthase activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Therefore, since (a) minor structural changes may result in changes affecting function, (b) there is no additional information correlating structure with the required function, (c) no information has been provided as to which amino acids in the helices of the polypeptide of SEQ ID NO:10 (or SEQ ID NO:8) can be modified and which ones need to be conserved to avoid loss of L-lysine transport activity, one

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cannot reasonably conclude that a polynucleotide encoding the polypeptide of SEQ ID NO: 10 (or SEQ ID NO:8) is representative of all the polynucleotides as required by the claims.

Due to the fact that the specification only discloses a single species of the genus of polynucleotides recited in the claims (i.e., SEQ ID NO:9) and a single species of the genus of proteins involved in secretion of L-lysine (i.e., L-lysine transport protein), and the lack of description of any additional species by any relevant, identifying characteristics or properties, one of skill in the art would not recognize from the disclosure that Applicant was in possession of the claimed invention.

18. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a *Methylobacillus glycogenes* bacterium which is able to produce L-lysine or L-arginine and is transformed such that it comprises and expresses the polynucleotide of SEQ ID NO: 9, does not reasonably provide enablement for a *Methylobacillus* bacterium able to produce L-lysine or L-arginine which comprises a DNA encoding a protein variant (1) comprising six hydrophobic helices, wherein said helices can have any amino acid sequence, and wherein said protein variant is involved in secretion of L-lysine to the outside of a methanol-assimilating bacterium, (2) which is a variant of a lysine transport protein, or (3) having any structure wherein said protein variant facilitates secretion of L-lysine and/or L-arginine to the outside of a methanol-assimilating bacterium. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400 (Fed. Cir. 1988)) as follows: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

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The factors which have lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed in detail below.

The breath of the claims. Claims 1-7 are so broad as to encompass *Methylobacillus* cells able to produce L-lysine or L-arginine, wherein DNA molecules have been introduced, wherein said DNA molecules (1) encode protein variants comprising six hydrophobic helices, wherein said helices can have any amino acid sequence, and wherein said protein variants are involved in secretion of L-lysine to the outside of a methanol-assimilating bacterium, (2) encode variants of a lysine transport protein, and (3) encode a protein having any structure wherein said protein facilitates secretion of L-lysine and/or L-arginine to the outside of a methanol-assimilating bacterium. See Claim Rejections under 35 USC 112, first and second paragraph, for claim interpretation and discussion of scope.

The enablement provided is not commensurate in scope with the claims due to the extremely large number of polynucleotides of unknown structure and function recited in the claims. In the instant case, the specification enables a *Methylobacillus glycogenes* bacterium which is able to produce L-lysine or L-arginine and is transformed such that it comprises and expresses the polynucleotide of SEQ ID NO:9.

The amount of direction or guidance presented and the existence of working examples. The specification discloses the amino acid sequence of the polypeptide of SEQ ID NO: 10 and the nucleotide sequence of the polynucleotide of SEQ ID NO: 9 as working examples. However, the specification fails to provide any information as to (1) the structural features required in any protein having six helices and involved in secretion of L-lysine to the extracellular medium, (2) the functions of all proteins as recited involved in secretion of L-lysine, or (3) the amino acids present in the helices of the polypeptide of SEQ ID NO:10 which are essential for the recited activity. As indicated above, one of skill in the art would not reasonably conclude that all that is required for a protein to be involved in L-lysine secretion is the presence of a hydrophobic helix. Thus, it is expected that the amino acid sequence of the helix would

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determine its activity. Furthermore, it is reiterated herein that while the claims encompass any protein associated in any way to L-lysine secretion, such as enhancers of L-lysine transport proteins or transcriptional activators, the specification discloses only an L-lysine transport protein. No correlation between structure and the recited activity has been provided.

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art. The nucleotide sequence of the coding region of a polynucleotide that encodes a protein determines the structural and functional properties of that protein. In the instant case, neither the specification nor the art provide a correlation between structure and activity such that one of skill in the art can envision the structure of any polynucleotide encoding a polypeptide having the same transporter function as that of the polypeptide of SEQ ID NO: 10. In addition, the art does not provide any teaching or guidance as to (1) which amino acids within SEQ ID NO: 10 can be modified and which ones are conserved such that one of skill in the art can make variants as recited encoding polypeptides with the same biological activity as that of the polypeptide of SEQ ID NO: 10, (2) which are the amino acid sequences of the helices in a protein that is involved in L-lysine secretion, (3) the general tolerance of L-lysine transport proteins to modification and the extent of such tolerance, (4) the identity/function of any protein involved in L-lysine secretion.

The art clearly teaches that changes in a protein's amino acid sequence to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein are required for that activity is highly unpredictable. At the time of the invention there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (Introduction to Protein Structure, Garland Publishing Inc., New York, page 247, 1991) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal

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how little is known about the rules of protein stability, and (3) the difficulties in designing *de novo* stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski et al. (Biochemistry 38:11643-11650, 1999) and Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) already discussed above, where it is shown that even small amino acid changes result in enzymatic activity changes. With regard to the *C. glutamicum* LysE gene product, the art as evidenced by Vrljic et al. (Molecular Microbiology 22:815-826, 1996; cited in the IDS) suggests that the configuration of the protein would enable the interaction of the protein with L-lysine's positive charge (page 821, left column). Thus, the art clearly suggests that the identity of the amino acids in the L-lysine transport protein is important for L-lysine to cross the cell membrane.

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification. While methods of generating or isolating variants of a polynucleotide were known in the art at the time of the invention, it was not routine in the art to screen by a trial and error process for the extremely large number of polynucleotides encompassed by the claims. Furthermore, it is not routine in the art to create variants of a polynucleotide encoding a protein having the activity recited, without any knowledge as to the structural features which would correlate with that activity. In the absence of a rational and predictable scheme for modifying any nucleotide of the polynucleotide of SEQ ID NO: 9, such that the resulting variant would encode a protein which retains the transporter activity of the polypeptide of SEQ ID NO: 10, and/or (2) a correlation between structure and the desired activity, one of skill in the art would have to test an essentially infinite number of polynucleotides to determine which ones encode proteins having the desired activity.

While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, as is the case herein, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed so that a reasonable number of species can be selected for testing. In view of the fact that such guidance has not been

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provided in the instant specification, it would require undue experimentation to enable the full scope of the claims.

Therefore, taking into consideration the extremely broad scope of the claims, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and function, and the high degree of unpredictability of the prior art in regard to structural changes and their effect on function, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Conclusion

19. No claim is in condition for allowance.

20. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.



Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652